**Supplemental Table:**

**Examples of Published Studies in Which Quantitative Histology Was Used To Advance Research in Celiac Disease**

|  |  |
| --- | --- |
| **Title & Reference** | **Use of Quantitative Histology** |
| *Dose dependent effects of protracted ingestion of small amounts of gliadin in coeliac disease children: a clinical and jejunal morphometric study**[Catassi C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Catassi%20C%5BAuthor%5D&cauthor=true&cauthor_uid=8244135) et al, 1993{Catassi, 1993 #1695}* | **Purpose:** To investigate the effects of ingestion of small amounts of gliadin (100 mg or 500mg daily) for 4 weeks on children with treated coeliac disease. **Main observations**: The authors reported a dose dependant reduction in Vh:Cd (100 mg group: 1.5 to 1.3, 500 mg group 1.6 to 1.1) and increase in IELs (100 mg group: 11 to 19, 500 mg group 10 to 25 IELs per 100 enterocytes) at the end of the 4 week gluten challenge.  |
| *Wheat Starch-Containing Gluten-Free Flour Products In The Treatment Of Coeliac Disease And Dermatitis Herpetiformis* *Kaukinen K et al, 1999 43* | **Purpose:** To determine whether wheat starch-based gluten-free products were safe to give to patients with celiac disease, children and adults with celiac disease and adults with dermatitis herptiformis (both groups on a GFD for a mean of 8 years), newly diagnosed patients with celiac disease (at diagnosis and on GFD for 6-24 months), and non-celiac patients with dyspepsia (controls). **Main observations**: Using quantitative histology, the authors showed that oral ingestion of wheat starch-based gluten-free products did not affect villus architecture, enterocyte high, IEL density, whereas patients with lapses in their GFD showed significant and quantifiable changes in Vh:Cd. |
| *Duodenal Histology In Patients With Celiac Disease After Treatment With A Gluten-Free Diet**Lee SK et al, 2003 44* | **Purpose:** Adult patient on a GFD for a mean of 8.5 years underwent review of paired (diagnostic and follow-up) biopsy samples using quantitative histology to assess the effectiveness of long-term gluten avoidance in patients with celiac disease. **Main observation**: Even with good clinical responses to the GFD, quantifiable histopathologic abnormalities persisted in the majority of patients. |
| *Oats In The Treatment Of Childhood Coeliac Disease: A 2-Year Controlled Trial And A Long-Term Clinical Follow-Up Study* *Holm K, 2006 et al 45* | **Purpose:** Quantitative histology used to assess the long-term safety of ingestion of oats in the treatment of pediatric patients with celiac disease over two years. Patients were randomized to receive either oats or a gluten challenge. At the time of histologic relapse with the gluten challenge, a GFD plus oats was started. After the trial, patients were allowed to continue ingesting oats with follow up extended for up to seven years.**Main observation:** Using quantitative histology, the authors demonstrated that oats did not induce any histologic or serologic changes over 2 years, whereas gluten-induced relapse was documented over 3-12 months. All patients who continued to eat oats remained in remission for up to 7 years. |

|  |  |
| --- | --- |
| *Clinical Trial: Gluten Micro-challenge With Wheat-Based Starch Hydrolysates In Coeliac Disease Patients—A Randomized, Double-Blind, Placebo-Controlled Study To Evaluate Safety* *Kaukinen K, 2008 et al 46* | **Purpose:** Use of quantitative histology in a randomized, placebo-controlled prospective follow up study of 90 pediatric patients with celiac disease (in clinical remission) to measure changes in mucosal morphology, IEL density and serology over 6 months in response to ingestion of wheat-based starch hydolysate products.**Main observation:** Vh:Cd, IEL densities (CD3+, +, + T lymphocytes) were measured at baseline and at 6 months; the use of these sensitive, reproducible measures allowed the authors to conclude that patients with celiac disease can safety consume wheat-based starch hydrolysates. |
| *Diagnosing Mild Enteropathy Celiac Disease: A Randomized, Controlled Clinical Study* *Kurppa K et al, 2009 47* | **Purpose:** Quantitative histology used to evaluate the effects of a GFD (vs. a gluten unrestricted diet) over time (1 year) on Vh:Cd in adult patients with mild enteropathy (by Marsh I, II). **Main observation**: Improvement in mucosal morphometric measures (i.e., Vh, Cd, IEL) and clinical symptoms in seropositive patients with baseline mild enteropathy on a GFD, was documented  |
| *Mucosal Recovery And Mortality In Adults With Celiac Disease After Treatment With A Gluten-Free Diet* *Rubio-Tapia A et al, 2010 40* | **Purpose:** To assess the rate of mucosal recovery after starting the GFD. 241 patients with partial to total villus atrophy at diagnostic biopsy who had follow-up biopsies 2-5 years after starting a GFD were evaluated by quantitative histology. **Main observation:**  Mucosal recovery, defined as a Vh:Cd ≥ 3.0, assessed by quantitative histology, was seen at 2 and 5 years in 34% and 66% of patients, respectively. The median time to confirmed mucosal improvement was 3.8 years.  |
| *Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease.* *Leffler D et al, 2010 5* | **Purpose:** To characterize the magnitude and the kinetics of symptomatic, histologic and serologic responses to oral gluten challenge in patients with treated celiac disease**Main observations:** Gluten challenge for 14 days at either 3g or 7.5g of gluten induced a significant reduction in Vh:Cd and increase in IELs at day 14. Celiac antibody titres increased slightly from baseline to day 14 but markedly by day 28. Gastrointestinal symptoms increased significantly by day 3 and returned to baseline by day 28. |
| *Morphometric Evaluation Of Duodenal Biopsies In Celiac Disease* *Cummins AG et al, 2011 42* | **Purpose:** To explore whether quantitative changes in histologic measures (i.e., villus area, crypt length) could provide better information than the Marsh classification on changes in duodenal morphology following introduction of a GFD. 57 adults with celiac disease were followed for up to 4 years with serial biopsies.**Main observations:** Morphometric data were found to be more sensitive than Marsh grade, and improvement in quantitative histology measures was significantly associated with improvement in anti-EMA titers.  |

|  |  |
| --- | --- |
| *Small- bowel mucosal changes and antibody responses after low- and moderate-dose gluten challenge in celiac disease.* *Lähdeaho ML et al, 2011 31*  | **Purpose:** To characterize small bowel mucosal histology changes and celiac antibody responses after oral gluten challenge. **Main observations:** Both moderate (3-5g per day) and low (1-3g) amounts of gluten induced small-bowel morphological damage in 67% of celiac patients after 12 weeks. Moderate gluten doses also triggered mucosal inflammation and more gastrointestinal symptoms. Celiac antibodies seroconverted in 43% of the patients. |
| *Glutenase ALV003 attenuates gluten-induced mucosal injury in patients with celiac disease.* *Lähdeaho ML et al 2014 6* | **Purpose: To** investigate the ability of ALV003, a mixture of 2 recombinant gluten-specific proteases given orally, to protect patients with celiac disease from mucosal injury during gluten challenge. **Main observation:** In this Phase 2 clinical trial the glutenase ALV003 appeared to attenuate gluten-induced small intestinal mucosal injury in patients with celiac disease exposed to up to 2 g gluten per day for 6 weeks. |